Tetrahedron Vol. 49, No. 36, pp. 7943-7954, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

The Cyclization Route to the Calcitriol A-ring: A Formal Synthesis of (+)-1α,25-Dihydroxyvitamin D_3

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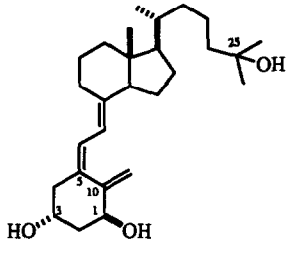
(*Received in USA* 19 *January* 1993; *accepted* 3 *March* 1993)

Abstract: An efficient asymmetric synthesis of the A-ring of 1α,25-dihydroxyvitamin D_3 from α-bromoacrolein is described. The key steps of the synthesis are the Evans type *syn*-selective asymmetric aldol reaction of bromoacrolein with the boron enolate of 3-chloroacetyl-4(S)-isopropyl oxazolidinone and ring closure by Heck type reaction of a vinyl bromide onto an α,β-unsaturated ester in the exo-mode.

This paper is warmly dedicated to Professor Sir Derek H. R. Barton, FRS, inventor of chemical reactions, scholar, teacher and mentor par excellence, on the happy occasion of his seventy-fifth birthday.

Although the total synthesis of (+)-1α,25-dihydroxyvitamin D_3 [(+)-calcitriol, **1**] was achieved in 1982 by the Baggiolini / Uskokovic team at Hoffmann-La Roche[1] interest in the synthetic chemistry of this essential metabolite of "vitamin D_3" has continued unabated, and has even grown reflecting the impetus provided by its multifaceted spectrum of biological activity.[2] In particular, the complexity and sensitivity of the A-ring moiety has attracted much attention and has served as the focal point for the development of much novel and elegant chemistry.[3,4]



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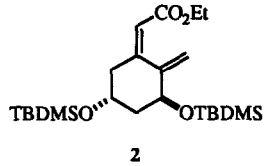

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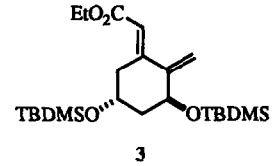
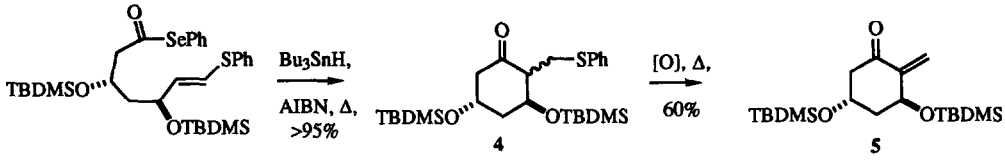


3

In this laboratory we have focused our efforts on the development of "the cyclization route" to the A-ring of calcitriol with the *Z*-diene ester **2**, or its *E*-isomer **3**, late stage intermediates in the Hoffmann-La Roche

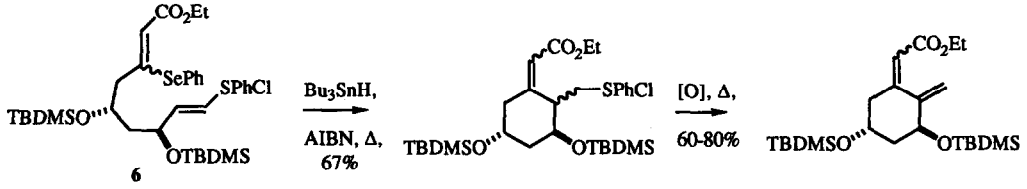
synthesis, as targets. The underlying philosophy called for application of the recent advances in acyclic stereoselection to the synthesis of a simple linear aliphatic molecule containing the two asymmetric secondary alcohols at C-1[5] and C-3, followed by a cyclization reaction with formation of the 5-10 bond. Very recently other groups, most notably that of Trost,[6b,c] have described the successful implementation of parallel cyclization strategies.[6]

Our initial studies, in the racemic series, were directed at acyl radical cyclizations and resulted in the ready formation of the A-ring ketone as indicated in Scheme 1.[7] These studies were especially important not only as the first successful synthesis of the A-ring of **1** from acyclic precursors, but also as they revealed the very significant accelerating effect of the anti-1,3-bissiloxy function on the cyclization reaction. Unfortunately, alkylideneation of the ketone **5** or its immediate precursor **4** could only be achieved in low yield,[8] so rendering the acyl radical cyclization route to calcitriol unattractive.



Scheme 1

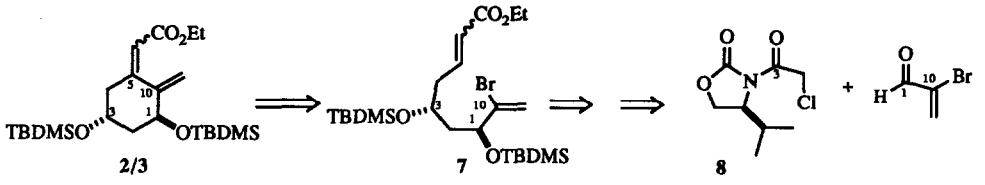
A successful, racemic synthesis of the diene ester **2** was subsequently developed through apendage of the extra two carbon atoms before cyclization, with the crucial ring closure now achieved by means of a vinyl radical (Scheme 2).[9] This synthesis, although successful, suffered from modest yields in the formation of the vinyl selenide (**6**), precursor to the vinyl radical. The poor yield in this step was mainly due to the steric bulk of the pendant chain and could not be overcome despite strenuous efforts.[8]



Scheme 2

A further, and more important problem, with this approach was uncovered when an asymmetric version was attempted. Thus, whereas the oxazolidinone **8**[10] could be condensed in high yield and excellent *syn*-selectivity with acrolein under the standard Evans conditions of Hunig's base / dibutylboron triflate[11] the same could not be said for condensation with the requisite trans-β-(4-chlorophenylthio)acrolein[12] with problems arising not only from poor *syn* / *anti* aldol ratios but also from the formation of *cis* / *trans* mixtures of the product alkene. Conversely, Heathcock reported in 1990 that high yields of *anti* adducts in the Evans aldol reaction could be achieved with β-arylthioacroleins when a two-fold excess of both dibutylboron triflate and triethylamine were used.[13] Consideration of these various factors led to a revised approach in which cyclization with formation of the vitamin D_3 5-10 bond would be achieved from the vinyl bromide **7** either with tributyltin hydride followed by formal dehydrogenation, or directly by an intramolecular Heck reaction (Scheme 3).[14]

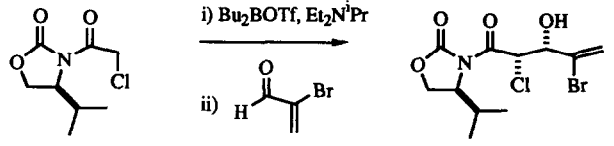
Preparation of the vinyl bromide (**7**) would be achieved by adaptation of the route used for the preparation of **6** with the correct asymmetry being introduced by means of an Evans aldol reaction with α-bromoacrolein.



Scheme 3

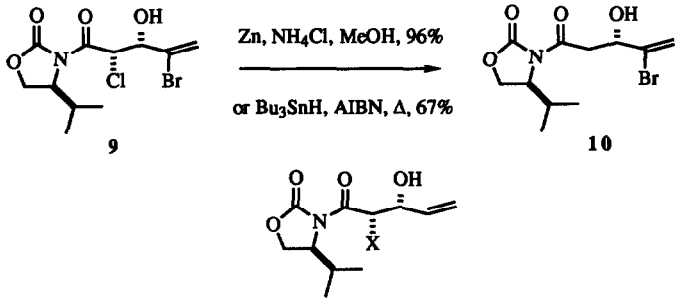
In addition to a number of successful 6-exo-trig vinyl radical cyclizations described in the literature[15] the cyclizations outlined in Schemes 2 and 3 boded well for the projected radical ring closure. Precedent for the formation of vicinal bis alkylidene cyclohexanes by intramolecular Heck reaction was drawn from the work of Grigg[16] as well as from that of Trost on the palladium mediated cyclization of enynes.[17]

The synthesis began with the Evans type aldol condensation of the L-valine derived chloroacetyl oxazolidinone **8** with α-bromoacrolein with the aid of dibutylboron triflate and Hunig's base resulting in the isolation of a single crystalline adduct **9** in 71% yield (Scheme 4). The relative and absolute stereochemistry of the two new stereocenters in **9** was assigned according to the standard Evans model for the aldol reactions of *Z*-boron enolates of propionyl oxazolidinones[11] as applied to **8** by Pridgen.[10,18] This assignment was ultimately confirmed by the identity of the final product with that synthesized by the Hoffmann-La Roche group. Mosher's ester analysis[19] of **9** revealed it to be a single compound within the limits of high field NMR (^1H, ^{13}C and ^{19}F) detection.



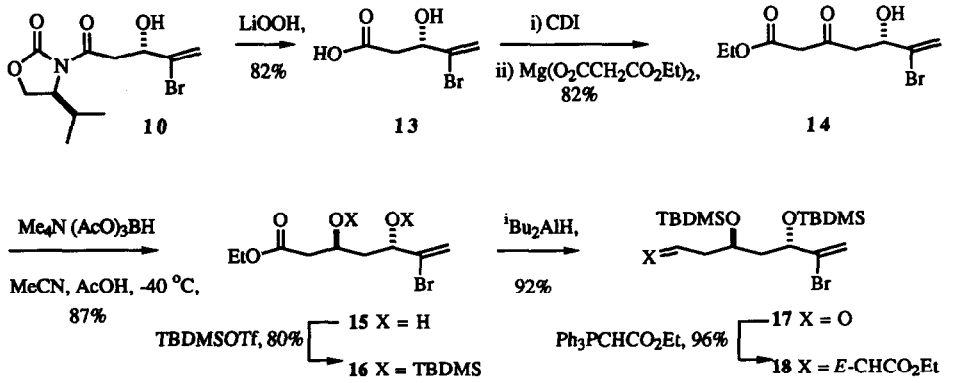
Scheme 4

Treatment of the aldol **9** with zinc powder and ammonium chloride in methanol overnight at room temperature cleanly afforded the dechloro product **10** in 96% isolated yield (Scheme 5). Interestingly, in view of the normal preference of stannyl radicals for attack at bromine over chlorine,[20] it was also possible to achieve the same transformation by heating to reflux with a 20% excess of tributyltin hydride and AIBN in benzene, resulting in isolation of **10** in 67% yield together with only 9% of the doubly dehalogenated product **11**. None of the product **12**, an authentic sample of which was available from condensation of **8** with acrolein, resulting from selective debromination was identified in the reaction mixture. This reversal of the normal selectivity was anticipated and readily explained in terms of the significantly greater stability of the delocalized radical formed on chlorine abstraction over the vinyl radical resulting from bromine abstraction. When two equivalents of tributyltin hydride were used **11** was isolated in 96% yield.



Scheme 5

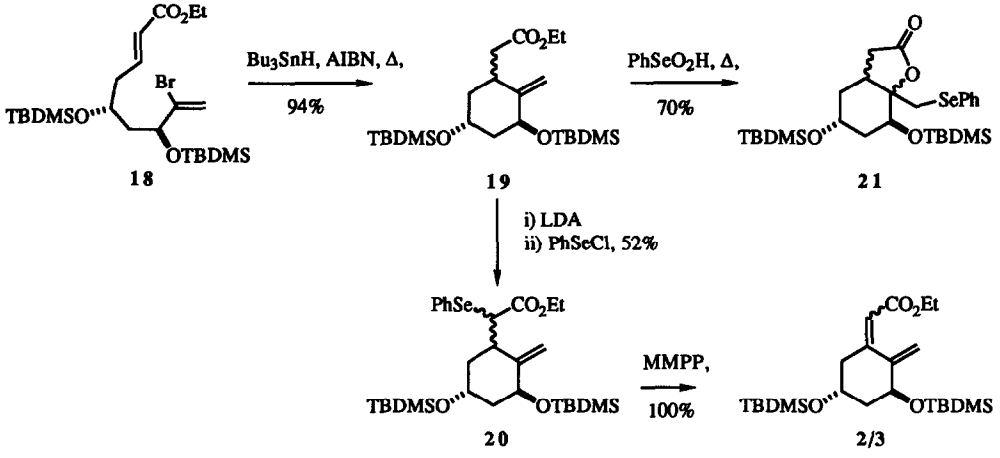
Subsequent steps involved saponification of **10** with lithium hydroperoxide according to the standard Evans protocol giving **13** in 82% yield followed by two carbon homologation by the Masamune procedure,[21] involving treatment with carbonyl diimidazolide and subsequently magnesium monoethyl malonate resulting in the isolation of **14** in 82% yield. Fortuitously, protection of the secondary alcohol was not necessary for the successful implementation of this reaction scheme (Scheme 6). The β-hydroxyketone **14** was then reduced with commercial tetramethylammonium triacetoxyborohydride[22] to give the anti-diol **15** in 87% yield as a 13:1 mixture with the *syn*-isomer. Protection was then achieved by reaction with *t*-butyldimethylsilyl triflate and pyridine in dichloromethane. After chromatographic separation of the minor *syn*-diastereoisomer, **16** was isolated in 80% yield. Silylation of **15** with TBDMS-Cl and imidazole in DMF was less satisfactory owing to the rather sluggish reaction of the second hydroxyl group with the result that the highest yield of **16** obtained in this manner was 61%. Dibal-H[R] reduction of **16** in toluene / dichloromethane at -78 °C was uneventful and provided the aldehyde **17** in 92% yield. Finally, the stage was set for cyclization when reaction of **17** with carboethoxymethylene triphenylphosphorane gave the Wittig product **18** in 96% isolated yield (Scheme 6).



Scheme 6

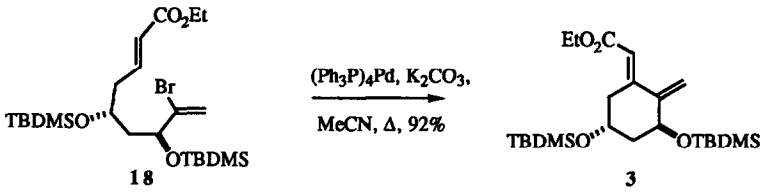
In the event treatment of **18** with tributyltin hydride and AIBN in benzene at reflux gave **19** in 94% isolated yield as a 1.2: 1 unassigned mixture of stereoisomers at the newly formed stereocenter (Scheme 7). Dehydrogenation was achieved by reaction with lithium diisopropylamide, then phenylselenyl chloride to give **20** in 52% isolated yield[23] followed by quantitative, oxidative syn-elimination with magnesium

monoperoxyphthalate (MMPP) in THF at room temperature. In this manner the target molecule was isolated as a 1.3:1 mixture of the *Z*- and *E*-isomers (Scheme 7). Dehydrogenation of **19**, prepared by an alternative route, has been achieved in 35-40% yield, via sulfoxide chemistry, by the Posner group.[4g] Attempted direct dehydrogenation of **19** by heating to 90 °C with benzeneseleninic acid[24] in chlorobenzene somewhat surprisingly resulted in the isolation of 70% of the lactone **21** and a number of unidentified minor products.



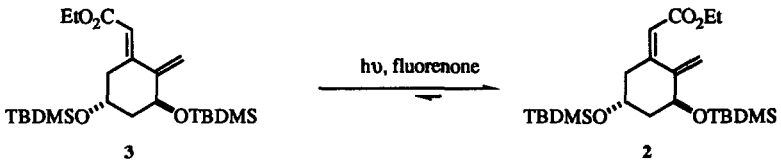
Scheme 7

The Pd^0 mediated cyclization of **18**, achieved by heating to reflux in acetonitrile with 5 mole % of tetrakis(triphenylphosphino)palladium and potassium carbonate, was much more efficient and resulted in the direct isolation, in 92% yield, of the *E*-isomer **3** of the target molecule (Scheme 8). Shortly after the completion of this project a Japanese group reported that a similar Pd^0 mediated cyclization of the (±)-*Z*-isomer of **18** led directly to the (±)-*Z*-diene ester **2** in excellent yield[6a] in accordance with the usual tenets[25] of *cis*-addition and *syn*-elimination of the Heck reaction.



Scheme 8

The formation of the *E*-isomer (**3**) in the Pd^0 mediated cyclization and of *E* / *Z* mixtures in the radical cyclization / dehydrogenation, is of no consequence as it is well appreciated in the field of vitamin D_3 chemistry that a photostationary equilibrium can be readily established between the two isomers and that the required *Z*-isomer is very substantially favored (Scheme 9). Indeed fluorenone sensitized isomerization of **3** to **2** was a key step (88% isolated yield) in the Hoffmann-La Roche synthesis of (+)-calcitriol (**1**).



3 2

Scheme 9

In conclusion we have provided a relatively concise asymmetric synthesis of of the the diene ester **3** that proceeds in 9 steps and 26 % overall yield from α-bromoacrolein in which the least efficient step is 71%. The diene ester **3** is a late stage intermediate in the Hoffmann synthesis of **1** and as such the work described constitutes a formal synthesis of (+)-calcitriol.

Acknowledgements: We thank the University of Illinois at Chicago for support, Mr A. Papadatos for extensive preliminary reactions, and for the preparation of compound **12**, and Mr M. Bruncko for assistance with the dehydrogenation of **19**.

EXPERIMENTAL SECTION

General. M.p.s are uncorrected and were determined with a Kofler hot stage microscope. Optical rotations were measured with a Perkin Elmer 241 polarimeter, $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded with a Perkin Elmer 1605 spectrophotometer. ^{1}H-NMR spectra were recorded at 300 MHz with a Bruker AC 300 instrument. ^{13}C-NMR spectra were recorded at 75 MHz with the same instrument operating in the ^{13}C mode. Chemical shifts (δ) are in ppm downfield from tetramethylsilane as internal standard, *J* values are given in Hz. 70 eV EIMS mass spectra were recorded with an AEI MS-30 mass spectrometer. Microanalyses were performed by Midwest Microanalytical, Indianapolis. All solvents were dried and distilled by standard techniques. Tetrahydrofuran (THF) was distilled under nitrogen from sodium benzophenone ketyl before use. Ether refers to diethyl ether and petroleum ether to the fraction boiling in the range 40-60 °C.

(+)-(4*S*)-3-[(2*S*,3*S*)-4-Bromo-2-chloro-3-hydroxypent-4-enoyl]-4-isopropyl-2-oxazolinone (9).- To a solution of the oxazolidinone **8**[10b] (410 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) stirred under Ar at -78 °C were added dropwise di-n-borontriflate in CH_2Cl_2 (1.0 M, 3.0 mL, 3.0 mmol) and then diisopropylethylamine (0.52 mL, 3 mmol). The reaction mixture was stirred at rt for 10 min and then at 0 °C for 30 min. It was then cooled to -78 °C and stirred for 30 min before addition of freshly distilled α-bromoacrolein[26] (340 mg, 2.5 mmol). After stirring for a further 30 min at -78 °C the reaction mixture was allowed to come to rt overnight and was then quenched a mixture of MeOH (10 mL) and pH 7 phosphate buffer (5 mL). 30% Aqueous hydrogen peroxide (10 mL) was then added dropwise at 0 °C and the resulting mixture stirred for 30 min before extraction with CH_2Cl_2 (3 x 50 mL). The extracts were dried (Na_2SO_4) and concentrated under reduced pressure and then purified by SiO_2 chromatography (EtOAc/petroleum ether 1/9 to 1/4) to give the aldol **9** as a colorless oil (483 mg, 71%) which solidified on standing. Crystallization from ether/petroleum ether gave white needles with m.p. 101-103 °C, $[\alpha]_D$ +78.3 (c = 0.006, acetone); δ_H: 0.91 (3 H, d, *J* = 6.6, C*H*$_3$CH$_3$CH), 0.93 (3 H, d, *J* = 6.6, CH$_3$C*H*$_3$CH), 2.40 (1 H, d. hept., *J* = 3.5 and 6.6, CH$_3$CH$_3$C*H*), 3.61 (1 H, d, *J* = 4.2, OH), 4.27 (1 H, dd, *J* = 8.8 and 3.2, H-5), 4.35 (1 H, dd, *J* = 8.8 and 8.0, H-5), 4.48 (1 H, ddd, *J* = 8.0, 3.5 and 3.0, H-4), 4.73 (1 H, m, C*H*OH), 5.76 (1 H, d, *J* = 2.2, =C*H*H),

6.04 (1 H, d, *J* = 4.2, C*H*Cl) and 6.16 (1 H, dd, *J* = 2.2 and 1.5, =CH*H*); δ_C: 14.62, 17.79, 29.97, 55.95, 58.54, 63.77, 74.57, 120.95, 128.51, 152.54 and 166.13; υ (film): 3480, 1784, 1708 and 1631 cm^{-1}; MS: 306 + 304 (M^+-Cl) and 262 + 260 (M^+-Br). Anal. Calcd. for $C_{11}H_{15}BrClNO_4$: C, 38.79; H, 4.44; N, 4.11. Found: C, 38.90; H, 4.39; N, 4.12%.

(+)-(4*S*)-3-[(3*S*)-4-Bromo-3-hydroxypent-4-enoyl]-4-isopropyl-2-oxazolinone (10) by Zn/NH_4Cl reduction of 9.- Aldol **9** (100 mg, 0.3 mmol) was dissolved in MeOH (5 mL) and treated with zinc powder (78 mg, 1.2 mmol) and NH_4Cl (65 mg, 1.2 mmol) and the suspension was vigorously stirred for 6 h at ambient temperature. Filtration, concentration and filtration on SiO_2 (EtOAc/petroleum ether 1/3) gave the title product as a colorless oil (87 mg, 96%) with $[\alpha]_D$ +57.9 (c=2.05, acetone); δ_H: 0.88 (3 H, d, *J* = 7.0, C*H*$_3$CH$_3$CH), 0.92 (3 H, d, *J* = 7.0, CH$_3$C*H*$_3$CH), 2.40 (1 H, m, CH$_3$CH$_3$C*H*), 3.27 (1 H, dd, *J* = 16.8 and 3.2, COC*H*H), 3.46 (1 H, dd, *J* = 16.8 and 8.8, COCH*H*), 3.52 (1 H, bs, OH), 4.22 (1 H, dd, *J* = 8.4 and 3.1, H-5), 4.28 (1 H, dd, *J* = 8.7 and 8.4, H-5), 4.45 (1 H, ddd, *J* = 8.4, 3.2 and 3.1, H-4), 4.64 (1 H, m, C*H*OH), 5.61 (1 H, d, *J* = 1.8, =C*H*H) and 6.03 (1 H, s, =C*H*H); δ_C: 14.67, 17.89, 28.42, 41.07, 58.53, 63.66, 72.25, 117.51, 134.38, 154.08 and 171.16; υ (film): 3431, 1783, 1700 and 1634 cm^{-1}; MS: 307 + 305 ($M^{+\cdot}$), 290 + 288 (M^+ - OH), 226 (M^+ - Br), 130 and 86.

Oxazolinone (10) and (+)-(4*S*)-3-[(3*S*)-3-Hydroxypent-4-enoyl]-4-isopropyl-2-oxazolinone (11) by Bu_3SnH reduction of 9.- A solution of **9** (34 mg, 0.1 mmol), Bu_3SnH (35 mg, 0.12 mmol) and AIBN (1 mg) in benzene (3 mL) was heated to reflux under N_2 for 3 h after which evaporation of the solvent and plc (SiO_2, EtOAc/hexanes 1/3) gave recovered **9** (R_f 0.43, 3 mg, 9%), the oxazolidinone **10** (R_f 0.36, 20 mg, 67%), and the oxazolidinone **11** (R_f 0.28, 2 mg, 9%). An authentic sample of **11** was prepared (96%) similarly, but using 2 equivalents of Bu_3SnH. It was a colorless oil with $[\alpha]_D$ +78.7 (c = 0.67, acetone); δ_H: 0.88 (3 H, d, *J* = 6.9, C*H*$_3$CH$_3$CH), 0.93 (3 H, d, *J* = 6.9, CH$_3$C*H*$_3$CH), 2.37 (1 H, d. hept., *J* = 6.9 and 3.6, CH$_3$CH$_3$C*H*), 3.11 (1 H, dd, *J* = 16.7 and 3.8, COC*H*H), 3.25 (1 H, dd, *J* = 16.7 and 8.5, COCH*H*), 4.23 (1 H, dd, *J* = 9.1 and 3.1, H-5), 4.30 (1 H, dd, *J* = 9.1 and 8.2, H-5), 4.46 (1 H, ddd, *J* = 8.2, 3.6 and 3.1, H-4), 4.60 (1 H, m, C*H*OH), 5.15 (1 H, dd, *J* = 10.6 and 1.3, =C*H*H), 5.32 (1 H, dd, *J* = 16.5 and 1.3, =C*H*H) and 5.93 (1 H, ddd, *J* = 16.5, 10.6 and 5.5, C*H*=CH$_2$); δ_C: 14.62, 17.85, 28.34, 42.21, 58.36, 63.58, 66.77, 115.12, 139.04, 154.06 and 171.60; υ (film): 3499, 1771 and 1695 cm^{-1}; MS: 227 (M^+), 210 (M^+ - OH), 209, 198, 171, 142, 130, 98 and 86.

(4*S*)-3-[(2*S*,3*R*)-2-Chloro-3-hydroxypent-4-enoyl]-4-isopropyl-2-oxazolinone (12). Preparation of an Authentic Sample.- To a solution of the oxazolidinone **8** (5.0 g, 24 mmol) in dry CH_2Cl_2 (70 mL) stirred under N_2 at 0 °C were added dropwise di-n-borontriflate in CH_2Cl_2 (1.0 M, 27 mL, 27 mmol) and then diisopropylethylamine (5.0 mL, 29 mmol). The reaction mixture was then cooled to -78 °C and treated dropwise with freshly distilled acrolein (2.0 mL, 26 mmol). The reaction mixture was maintained at -78 °C with stirring for 30 min then allowed to warm to rt and stirred for a further 1.5 h before addition of MeOH (120 mL), pH 7 phosphate buffer (57 mL) and finally, at 0 °C, 30% H_2O_2 (57 mL). After stirring for 1 h more at 0 °C the reaction mixture was exhaustively extracted with ether and the extracts washed with water, and brine and dried ($MgSO_4$) before concentration. After chromatography (SiO_2, ether/petroleum ether 1/1) the aldol **12** was obtained as a pale yellow oil (4.0 g, 66%) with δ_H: 0.91 (3 H, d, *J* = 6.6, C*H*$_3$CH$_3$CH), 0.92 (3 H, d, *J* = 6.6, CH$_3$C*H*$_3$CH), 2.38 (1 H, d. hept., *J* = 4.0, 6.6, CH$_3$CH$_3$C*H*), 3.02 (1 H, bs, OH), 4.24 (1 H, dd, *J* = 9.0 and 3.8, H-5), 4.31 (1 H, dd, *J* = 9.0 and 9.0, H-5), 4.45 (1 H, ddd, *J* = 9.0, 4.0 and 3.8, H-4), 4.62 (1

H, m, C*H*OH), 5.29 (1 H, d, *J* = 10.4, =C*H*H), 5.42 (1 H, d, *J* = 17.0, =CH*H*), 5.67 (1 H, d, *J* = 4.7, C*H*Cl) and 5.87 (1 H, ddd, *J* = 17.0, 10.4 and 5.5, C*H*=CH_2); δ_C: 14.66, 17.74, 28.12, 58.50, 58.65, 63.75, 72.34, 118.58, 135.12, 152.66 and 168.02; υ (film): 3560, 1784 and 1708 cm^{-1}. HRMS: Calcd. for $C_{11}H_{16}ClNO_4$: 261.0767. Found: 261.0768.

(+)-(3*S*)-4-Bromo-3-hydroxypent-4-enoic Acid (13).- Oxazolidinone **10** (305 mg, 1.0 mmol) in THF (8 mL) and water (2 mL) was treated at rt with 30% H_2O_2 (1 mL) and LiOH (48 mg, 2 mmol) and stirred for 1.5 h before the reaction was quenched by addition of Na_2SO_3 (1.0 g). THF was then removed under vacuum and the remaining aqueous phase basified to pH 9-10 with 5% $NaHCO_3$. Extraction with CH_2Cl_2 enabled recovery of the chiral auxiliary (~90%). Subsequent acidification of the aqueous phase with 10% HCl to pH ~2 and extraction with EtOAc, drying ($MgSO_4$) and concentration gave the crude acid **13**. Chromatography (SiO_2, MeOH/EtOAc 1/99) gave the pure title compound as a colorless oil (160 mg, 82%) with $[\alpha]_D$ +5.1 (c = 2.5, acetone); δ_H: 2.68 (1 H, dd, *J* = 16.2 and 8.8, H-2), 2.84 (1 H, dd, *J* = 16.2 and 3.6, H-2), 4.63 (1 H, dd, *J* = 8.8 and 3.6, H-3), 5.61 (1 H, d, *J* = 1.9, H-5), 6.02 (1 H, s, H-5) and 7.20 (2 H, bs, CO_2H + OH); δ_C: 40.11, 72.10, 117.64, 133.98 and 175.50; υ (film): 3300, 1717 and 1630 cm^{-1}; MS: 196 + 194 (M^+·), 179 + 177 (M^+ - OH), 178 + 176 (M^+ - H_2O) 173 + 135, 136 + 134, 115 (M^+ - Br), 97 and 55.

(+)-Ethyl (5*S*)-6-Bromo-5-hydroxy-3-ketohept-6-enoate (14).- Carbonyl diimidazole (425 mg, 2.62 mmol) was added in one portion to a solution of the acid **13** (464 mg, 2.38 mmol) in dry THF (20 mL) resulting in a slightly exothermic reaction. After stirring at rt for 6 h the magnesium salt of monoethyl malonate,[21] prepared from monoethyl malonate[27] and magnesium ethoxide, (755 mg, 2.62 mmol) was added. After stirring at rt for 16 h and evaporation of THF the reaction mixture was treated with 0.5 N HCl and ether extracted (3 x 30 mL). The extracts were washed with 5% $NaHCO_3$, dried ($MgSO_4$) and concentrated to give a yellow oil, purification of which by SiO_2 chromatography (EtOAc/petroleum ether 1/4) gave the title ester as a colorless oil (520 mg, 82%). This somewhat unstable substance had $[\alpha]_D$ +2.2 (c = 1.4, acetone); δ_H: 1.28 (3 H, t, *J* = 7.2, *Me*CH_2), 2.88 (1 H, dd, *J* = 17.0 and 8.4, H-4), 2.99 (1 H, dd, *J* = 17.0 and 3.5, H-4), 3.54 (2 H, s, H-2), 4.19 (2 H, q, MeC*H*$_2$), 4.66 (1 H, dd, *J* = 8.4 and 3.5, H-5), 5.05 (1 H, bs, OH), 5.56 (1 H, d, *J* = 1.3, H-7) and 6.02 (1 H, bs, H-7); δ_C: 14.09, 48.13, 49.93, 61.52, 71.47, 117.37, 134.91, 167.08 and 201.56; υ (film): 3458, 1734, 1718 and 1633 cm^{-1}; MS: 248 + 246 (M^+ - H_2O), 220 + 218, 167 (M^+ - Br-H_2O), 115 and 87.

Ethyl (3*S*,5*S*)-6-Bromo-3,5-dihydroxyhept-6-enoate (15).- To a stirred solution of Me_4N^+ $B(OAc)_3H^-$ (400 mg, 1.5 mmol) in MeCN (5 mL) and AcOH (0.5 mL) under N_2 at -40 °C was added dropwise a solution of **14** (100 mg, 0.38 mmol) in MeCN (1 mL). The reaction mixture was maintained at -40 °C for 0.5 h then allowed to warm to rt overnight. The reaction was quenched by addition of saturated $NaHCO_3$ solution, then extracted with EtOAc. The extracts were dried ($MgSO_4$), concentrated and purified by SiO_2 chromatography (EtOAc/petroleum ether 1/3) to give the diol **15** as a colorless oil (87 mg, 87%) as a 13:1 mixture with its *syn*-isomer as estimated by ^{1}H-NMR. The diol **15**, which decomposed slowly on standing at room temperature, had δ_H: 1.28 (3 H, t, *J* = 7.1, *Me*CH_2), 1.89 (2 H, dd, *J* = 6.1 and 5.1, H-4), 2.51 (2 H, d, *J* = 5.9, H-2), 3.77 (2 H, bs, 2 x OH), 4.18 (2 H, q, *J* = 7.1, MeC*H*$_2$), 4.34 (1 H, tt, *J* = 5.9 and 5.1, H-3), 4.47 (1 H, t, *J* = 6.1, H-5), 5.61 (1 H, s, H-7) and 6.05 (1 H, s, H-7); δ_C: 14.27, 39.77, 41.32, 61.05, 65.37, 73.46, 116.77, 135.97 and 172.87; υ (film): 3427, 1717 and 1628 cm^{-1}; MS: 250 + 248 (M^+ - H_2O), 169 (M^+ - Br - H_2O), 135 and 71.

Ethyl (3*S*,5*S*)-3,5-Bis(*t*-butyldimethylsiloxy)-6-Bromohept-6-enoate (16).- To a stirred solution of the diol **15** (106 mg, 0.4 mmol) and pyridine (126 mg, 1,6 mmol) in dry CH_2Cl_2 (8.0 mL) under N_2 at 0 °C was added dropwise TBDMS-OTf (264 mg, 1.0 mmol) followed by stirring at 0 °C for 0.5 h then at rt for 0.5 h. The reaction was quenched by addition of NH_4Cl solution and extracted with ether. The extracts were washed with water, dried ($MgSO_4$), concentrated and chromatographed (SiO_2, EtOAc/hexanes 1/9) to give the title ester as a colorless oil (158 mg, 80%) with δ_H: 0.06 (3 H, s, MeSi), 0.07 (3 H, s, MeSi), 0.10 (3 H, s, MeSi), 0.11 (3 H, s, MeSi), 0.87 (9 H, s, Me_3C), 0.91 (9 H, s, Me_3C), 1.26 (3 H, t, J = 7.1, $MeCH_2$), 1.80 (1 H, ddd, J = 14.2, 7.0 and 6.9, H-4), 1.89 (1 H, ddd, J = 14.2, 5.3 and 5.1, H-4), 2.46 (1 H, dd, J = 14.4 and 7.0, H-2), 2.52 (1 H, dd, J = 14.4 and 5.3, H-2), 4.11 (2 H, bq, J = 7.1, $MeCH_2$), 4.21 (1 H, tt, J = 7.0 and 5.3, H-3) 4.24 (1 H, dd, J = 6.9 and 5.1, H-5), 5.53 (1 H, d, J = 1.6, H-7) and 5.84 (1 H, t, J = 1.0, H-7); δ_C: -4.94, -4.49, -4.25 (2C), 14.17, 17.93, 25.73 (6 x Me_3C), 43.32, 44.81, 60.27, 66.91, 74.08, 116.70, 136.06 and 171.21; υ (film): 1738 and 1625 cm^{-1}; MS: 481 + 479 (M^+ - Me), 439 + 437 (M^+ - Me_3C), 189 and 147. HRMS: Calcd. for $C_{20}H_{40}BrO_4Si_2$ (M^+ - Me): 479.1649. Found: 479.1658.

(3*S*,5*S*)-3,5-Bis(*t*-butyldimethylsiloxy)-6-Bromohept-6-enal (17).- To a solution of the ester **16** (250 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) stirred at -78 °C under N_2 was added a solution of Dibal-H in toluene (1 M, 0.6 mL, 0.6 mmol) dropwise. Stirring was continued at -78 °C for 0.5 h before MeOH (0.5 mL) and then aqueous sodium potassium tartrate (0.5 M, 5 mL) were added. After stirring vigorously for a further 10 min at rt the reaction mixture was extracted with ether, the extracts dried ($MgSO_4$), concentrated under vacuum and purified by chromatography on SiO_2 (EtOAc/petroleum ether 1/9) to give the title aldehyde as a colorless oil (207 mg, 90%) with δ_H: 0.06 (6 H, s, 2 x MeSi), 0.07 (3 H, s, MeSi), 0.10 (3 H, s, MeSi), 0.85 (9 H, s, Me_3C), 0.89 (9 H, s, Me_3C), 1.82 (1 H, ddd, J = 14.0, 7.1 and 6.8, H-4), 1.94 (1 H, ddd, J = 14.0, 5.6 and 5.2, H-4), 2.56 (2 H, m, H-2), 4.21 (1 H, t, J = 5.9, H-5), 4.27 (1 H, tt, J = 6.0 and 5.7, H-3), 5.51 (1 H, s, H-7), 5.83 (1 H, s, H-7) and 9.79 (1 H, t, J = 2.4, H-1); δ_C: -4.95, -4.69, -2.98 (2 x MeSi), 17.91, 18.08, 25.74 (6 x Me_3C), 44.74, 51.10, 65.50, 73.95, 116.91, 137.75 and 201.46; υ (film): 2712, 1728 and 1616 cm^{-1}; MS: 437 + 435 (M^+ - Me), 395 + 393 (M^+ - Me_3C), 189 and 147.

(+)-Ethyl (5*S*,7*S*)-5,7-Bis(*t*-butyldimethylsiloxy)-8-Bromonona-2*E*,8-dienoate (18).- The aldehyde **17** (450 mg, 1 mmol) was treated in benzene at rt with carboethoxymethylene triphenylphosphorane (520 mg, 1.2 mmol) and the resulting mixture stirred overnight at rt. The solvent was evaporated under vacuum and the residue purified by chromatography on SiO_2 (EtOAc/hexanes 2/98) to give the enone **18** as a colorless oil (500 mg, 96%) with $[\alpha]_D$ +1.6 (c = 1.1, acetone); δ_H: 0.03 (6 H, s, 2 x MeSi), 0.04 (3 H, s, MeSi), 0.05 (3 H, s, MeSi), 0.85 (9 H, s, Me_3C), 0.86 (9 H, s, Me_3C), 1.23 (3 H, t, J = 7.1, $MeCH_2$), 1.70 (1 H, ddd, J = 14.2, 6.8 and 6.5, H-6), 1.77 (1 H, ddd, J = 14.2, 5.6 and 5.2, H-6), 2.30 (1 H, ddd, J = 14.4, 7.3 and 6.5, H-4), 2.39 (1 H, ddd, J = 14.4, 7.2 and 6.8, H-4), 3.84 (1 H, tt, J = 6.8 and 6.5, H-5), 4.14 (2 H, q, J = 7.1, $MeCH_2$), 4.16 (1 H, t, J = 5.5, H-7), 5.46 (1 H, d, J = 1.4, H-9), 5.78 (1 H, s, H-9), 5.80 (1 H, d, J = 15.7, H-2) and 6.91 (1 H, dt, J = 15.7 and 7.3, H-3); δ_C: -4.97, -4.44, -4.26, -4.07, 14.26, 18.03, 18.11, 25.77, 25.82, 40.44, 44.73, 60.12, 66.50, 74.11, 116.67, 125.59, 138.17, 145.31 and 166.25; υ (film): 1725, 1657 and 1625 cm^{-1}; MS: 507 + 505 (M^+ - Me), 465 + 463 (M^+ - Me_3C), 409 + 407 (M^+ - $EtO_2CCH{=}CHCH_2$), 331, 251 + 249, 147 and 73. HRMS: Calcd. for $C_{22}H_{42}BrO_4Si_2$: 505.1805 (M^+ - Me). Found: 505.1807.

(1*RS*,3*S*,5*R*)-3,5-Bis(*t*-butyldimethylsiloxy)-1-carboethoxymethyl-2-methylene-cyclohexane (19).- A solution of the α,β-unsaturated ester **18** (52 mg, 0.1 mmol) and Bu_3SnH (35 mg, 0.12 mmol) and AIBN (3 mg) in benzene (3 mL) was heated to reflux under N_2 for 0.5 h. After cooling to rt the solution was poured onto a silica gel column. Elution with EtOAc/hexanes 2/98 gave the cyclization product **19**,[6g] a colorless oil (42 mg, 94%), as an ~2:1 mixture of stereoisomers as determined by ^{1}H-NMR. The major isomer had δ_H: 0.45 (12 H, s, MeSi), 0.88 (18 H, s, Me_3C), 1.24 (3 H, t, J = 7.1, $MeCH_2$), 1.3-1.8 (2 H, m, 2 x H-6), 1.91 (2 H, m, 2 x H-4), 2.39 (1 H, dd, J = 15.3 and 7.6, CH_2CO_2Et), 2.59 (1 H, dd, J = 15.3 and 7.3, CH_2CO_2Et), 2.98 (1 H, m, H-1), 4.13 (2 H, q, J = 7.1, $MeCH_2$), 4.22 (1 H, m, H-5), 4.38 (1 H, dd, J = 5.2 and 3.0, H-7), 4.65 (1 H, s, =CHH) and 4.84 (1 H, s, =CHH). The minor isomer had δ_H: 0.50 (12 H, s, MeSi), 0.90 (18 H, s, Me_3C), 1.24 (3 H, t, J = 7.1, $MeCH_2$), 1.3-1.8 (2 H, m, 2 x H-6), 1.91 (2 H, m, 2 x H-4), 2.30 (1 H, dd, J = 14.9 and 9.0, CH_2CO_2Et), 2.66 (1 H, dd, J = 14.9 and 5.8, CH_2CO_2Et), 2.98 (1 H, m, H-1), 4.10 (2 H, q, J = 7.1, $MeCH_2$), 4.22 (1 H, m, H-5), 4.43 (1 H, dd, J = 11.0 and 4.9, H-3), 4.64 (1 H, s, =CHH) and 5.05 (1 H, s, =CHH). The mixture was further characterized by υ (film): 1738 and 1651 cm^{-1}; MS: 427 (M^+ - Me), 397 (M^+ - EtO), 385 (M^+-Me_3C), 313, 253, 165, 105 and 73.

(-)-(1*E*,3*S*,5*R*)-3,5-Bis(*t*-butyldimethylsiloxy)-1-carboethoxymethylene-2-methylene-cyclohexane (3) by Intramolecular Heck Reaction on 18.- A mixture of **18** (104 mg, 0.2 mmol), K_2CO_3 (140 mg, 1.0 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) in MeCN (15 mL) was heated to reflux under N_2 for 30 h. The cooled solution was then filtered on a short SiO_2 plug eluting with CH_2Cl_2 and then chromatographed on SiO_2 (EtOAc/hexanes 1/9) to give the pure *E*-isomer (**3**) of the target compound as a colorless oil (81 mg, 92%) with $[\alpha]_D$ -4.2 (c = 0.48, EtOH), lit.[1] $[\alpha]_D$ -4.7 (c = 0.5, EtOH), δ_H: 0.06 (6 H, s, MeSi), 0.07 (6 H, s, MeSi), 0.87 (9 H, s, Me_3C), 0.91 (9 H, s, Me_3C), 1.29 (3 H, t, J = 7.1, $MeCH_2$), 1.77 (1 H, ddd, J = 12.3, 9.6 and 2.3, H-4), 1.98 (1 H, ddd, J = 12.3, 4.5 and 4.3, H-4), 2.67 (1 H, d, J = 14.9, H-6), 3.39 (1 H, dd, J = 14.9 and 5.4, H-6), 4.15 (2 H, q, J = 7.1, $MeCH_2$), 4.27 (1 H, ddd, J = 5.4, 4.3 and 2.3, H-5), 4.58 (1 H, dd, J = 9.6 and 4.5, H-3), 5.08 (1 H, s, =CHH), 5.10 (1 H, s, =CHH) and 5.92 (1 H, s, $=CHCO_2Et$), lit.[1] (100 MHz): 0.06 (12 H, s), 0.86 (9 H, s), 0.90 (9 H, s), 1.27 (3 H, t), 2.66 (1 H, bd, J = 10.6), 3.36 (1 H, bdd, J = 10.6 and 5.4), 4.16 (2 H, q), 4.25 (1 H, bm), 4.58 (1 H, bm), 5.07 (2 H, bs), 5.89 (1 H, bs); δ_C: -5.04 (2 x MeSi), -4.88 (2 x MeSi), 14.31, 18.04, 18.22, 25.67, 25.79, 37.42, 43.65, 59.70, 67.09, 70.06, 109.72, 116.46, 152.08, 157.05 and 166.51; υ (film): 1718 and 1640 cm^{-1}; MS: 440 (M^+), 425(M^+-Me), 395(M^+-EtO), 384 (M^+ + 1 - Me_3C), 383 (M^+ - Me_3C), 251 and 73.

Compounds 2 and 3 by Dehydrogenation of 19.- To a solution of **19** (35 mg, 0.08 mmol) in THF (0.5 mL) under N_2 at -78 °C was added a solution of LDA in THF (0.5M, 0.24 mL, 0.12 mmol). After stirring for 30 min PhSeCl (30 mg, 0.15 mmol) in THF (0.25 mL) was added, the reaction mixture was then stirred at -78 °C for 1h, allowed to warm to rt and quenched by addition of saturated aqueous NH_4Cl (1 mL) then water (2 mL), extracted with CH_2Cl_2 and the extracts dried ($MgSO_4$) and concentrated under vacuum. Preparative tlc (SiO_2, ether/petroleum ether 1/20) then yielded the selenide **20** (25 mg, 52%) and recovered **19** (10 mg, 29%). The selenide **20** (10 mg, 0.017 mmol), a complex mixture of 4 diastereoisomers, was then dissolved in THF (3.5 mL) and treated with MMPP (9 mg, 0.018 mmol) at room temperature with stirring for 2 h. The reaction mixture was then poured directly onto a SiO_2 column, elution of which with CH_2Cl_2 gave the target molecule as a 1:1.3 mixture of its *E*- and *Z*-isomers (**3** and **2**) in the form of a colorless oil (7.5 mg, 100%). The ^{1}H-NMR spectrum of the *E*-isomer coincided exactly with that described above whereas the *Z*-

isomer (2) had δ_H: 0.06 (6 H, s, MeSi), 0.08 (6 H, s, MeSi), 0.85 (9 H, s, Me_3C), 0.88 (9 H, s, Me_3C), 1.25 (3 H, t, J = 7.0, $MeCH_2$), 1.80 (1 H, m, H-4), 1.96 (1 H, m, H-4), 2.24 (1 H, dd, J = 11.1 and 5.6, H-6), 2.40 (1 H, d, J = 11.1, H-6), 4.08 (2 H, m, $MeCH_2$), 4.23 (1 H, m, H-5), 4.53 (1 H, m, H-3), 5.07 (1 H, m, =C*H*H), 5.18 (1 H, m, =CH*H*) and 5.62 (1 H, s, =C*H*CO_2Et), lit.[1] (100 MHz): 0.05 (6 H, s), 0.09 (6 H, s), 0.86 (9 H, s), 0.89 (9 H, s), 1.24 (3 H, t), 4.10 (2 H, q), 4.22 (1 H, bm), 4.51 (1 H, bm), 5.02 (1 H, bs), 5.18 (1 H, bs), 5.62 (1 H, bs).

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